REMARKS

Favorable consideration and allowance are respectfully requested for claims 2-5 and 9-16 in view of the foregoing amendments and remarks.

New claim 16 is submitted herewith and is directed to a polynucleotide comprising a nucleic acid sequence selected from the nucleotide sequence included in the plasmid pSgs4 deposited in *S. lividans* strain TK24/pSgs4 with the accession number DSM 12998 and the nucleotide sequence included in the plasmid pSgc5 deposited in *E. coli* strain XL1BlueMRF'/pSgc5 with the accession number DSM 12999. This claim is supported in the specification on the paragraph bridging pages 10 and 11 and the first paragraph on page 13 and includes no new matter.

In the Office Action dated February 11, 2004, the Examiner maintained the restriction requirement. Applicants respectfully request reconsideration of this determination, as it is improper. The Examiner considers that one gene is one invention, and the individual functions of genes that are useful independent of producing a final product render them distinct inventions. However, all of the genes in the present gene cluster are not functional alone. The genes in the cluster are organized into operons, wherein many of the predicted translational initiative and termination sites are either overlapping or lying extremely close together, suggesting that many of the genes are translationally coupled.

Therefore, use of the natural arrangement and native promoters within the gene cluster allows enhanced expression of the genes.

It is a well-known fact that in antibiotic biosynthetic gene clusters, single genes are expressed in higher levels in large DNA fragments than when in isolated fragments. Consequently, it is more probable that the whole cluster or large DNA fragment is useful for exploitation of the cloned genes. Although the function of an individual gene may be interesting from an academic or scientific perspective, the production of maximal yields is both required and expected for commercial applications. Those fragments resulting in higher titers of desired products are greatly preferred. Therefore, the individual genes should not be separated from the cluster into individual inventions, rather the cluster should be considered as a unity including the series of mutually connected fragments, which should be together.

Moreover, the law allows the patent applicant to be his or her lexicographer and to claim his or her invention as he or she sees fit. Accordingly, the U.S. Patent and Trademark Office should not require restriction, especially where such restriction might result a lesser claim coverage. Applicants have a statutory right to claim what they regard as their invention and where the proposed groupings of a restriction are not coextensive with the invention as claimed by the Applicant, the restriction is improper. The present restriction is precisely the type of degradation of Applicants' statutory right which the law

does not permit. Accordingly, in response to paragraphs 1 and 2 of the Office Action, Applicants respectfully request reconsideration of the Restriction Requirement.

The Examiner requested that Applicants provide a copy of the claims from the official Priority Document, foreign application 19992085 filed on September 29, 1999, to show the recitation of 84% homology as recited in claims 2,-3 and 9-15. A certified copy of pages 39 and 40 of the claims from this application is submitted with this response as Appendix A. Support for the 84% homology is provided in claim 2 of these originally submitted claims.

The specification was objected to for allegedly lacking clarity in its examples, in particular with respect to how the primers used in cloning the gene cluster were formulated . While Applicants maintain that the examples provided in the specification are of sufficient clarity, for purposes of complying with the Examiner's request, Applicants wish to point out the biosynthetic aclacinomycins contain deoxysugars. Therefore, Applicants used a gene fragment involved in the first reactions of the deoxyhexose pathway, and in particular a conserved sequence. This sequence has been published by Decker *et al.* (Decker H., Gaisser S., Pelzer, S., Schneider P., Westrich L., Wohlleben W. and Bechthold A. (1996) A General Approach for Cloning and Characterizing dNDP-Glucose Dehydratase Genes from Actinomycetes. FEMS Microdiol LETT. 141: 195-201. The accepted manuscript of this document is enclosed as Appendix B.

Claims 2-3 and 9-15 were objected to for being drawn to non-elected subject matter. As suggested by the Examiner, Applicants have amended these claims to delete the recitation of "or part thereof having similar characteristics." Accordingly, withdrawal of this objection is respectfully requested.

Claims 1, 3 and 9-15 were rejected under 35 U.S.C. § 112, second paragraph as indefinite. This rejection is respectfully traversed. In particular, the Examiner stated that the term "anthracycline biosynthetic pathway" is unclear. Applicants have deleted claim 1 so that the allegedly problematic term no longer appears in the claims. Accordingly, withdrawal of this rejection is respectfully requested.

Claims 2, 3 and 9-15 were objected to under 35 U.S.C. § 112, second paragraph as indefinite for citing the term "84% homology." Clarification of this term is provided by way of a declaration under 37 C.F.R. § 1.132 by Kaj Räty, one of the inventors, which is submitted herewith. As evident from the declaration, it is a routine procedure for the present inventors to make an identity search for the sequences found in their studies. On the basis of the results obtained, an appropriate homology percentage is determined for each case. This explanation provides suitable clarification of the term "84% homology" so as to clearly define the metes and bounds of the claim.

Claim 3 was rejected under 35 U.S.C. §112, second paragraph as indefinite. The claim has been amended to recite "said DNA fragment" and "a

plasmid replicating" as suggested by the Examiner. Accordingly, withdrawal of this rejection is respectfully requested.

Claims 12, 13 and 15 were rejected under 35 U.S.C. § 112, second paragraph, as indefinite in reciting the terms "metabolites" and "anthracycline metabolites." This rejection is respectfully traversed. Claim 12 has been amended to replace the word "metabolites" by "polyketides." With regard to the term "anthracycline metabolites" in claim 13, the scientific community has used this term from at least the year 1986. Abstracts from three journal articles are provided herewith as Appendix C. Each of these abstracts recites the phrase "anthracycline metabolites." Accordingly, Applicants submit that this phrase has a clear and definite meaning to a person of skill in the art. Reconsideration and withdrawal of this rejection are respectfully requested.

Claims 14 and 15 were rejected under 35 U.S.C. § 112 as indefinite in reciting the terms "activator" and "polyketide assembler." The term "activator" refers to a positive regulator of antibiotic biosynthesis. In this case, it means a gene product, which activates expression of genes in the biosynthesis cluster by binding DNA in the promoter sequence (for references see for example, Appendix D, in particular Ylihonko, K., Tuikkanen, J., Jussila, S., Cong L., and Mantsala, P. A Gene Cluster Involved in Nogalamycin Biosynthesis From *Streptomyces Nogalater*: Sequence Analysis and Complimentation of Early-Block Mutations in the Anthracycline Pathway. Mol Gen Genet 251:113-112 (1996) and Tang, L.,

Grimm A., Zhang Y. and Hutchinson R. Purification and Characterization of the DNA-binding protein DNRI, a Transcriptional Factor of Daunorubicin Biosynthesis in *Streptomyces, Peucetius* Molecular Microbiology 22(5): 801-813 (1996). Thus, the term "activator" has a clear and definite meaning to a person of skill in the art as evidenced by the use of this term in these references.

Further, the term "polyketide assembler" means an enzyme related to the assembling of a polyketide chain. For example, the phrase "polyketide chain assembly" is used in the review article by Hopwood, D.A. Genetic Contributions to Understanding Polyketide Syntheses, Chemical Reviews, 97:2465-2497 (1997), which is attached as Appendix E. Thus, a "polyketide assembler" is any enzyme useful when related to the assembly of such a polyketide chain. The use of these terms in the listed articles clearly demonstrates that the terms have a definite and understandable meaning to a person of skill in the art. Accordingly, reconsideration and withdrawal of the rejection of claims 14 and 15 are respectfully requested.

Claims 1 and 9-15 were objected to under 35 U.S.C. § 112, first paragraph, because claim 1 is allegedly drawn to a DNA fragment without any definite structural limitations. Claim 1 has been deleted by this amendment. Accordingly, withdrawal of this rejection is respectfully requested.

Claims 2, 3 and 9-15 were rejected under 35 U.S.C. § 112, first paragraph, for allegedly reciting a genus containing DNA fragments within the sequence

identity limitations, but having different function. By this amendment, the reference to the partial sequence is deleted. Accordingly, this rejection under paragraph 13 of the Office Action is no longer applicable and withdrawal thereof is respectfully requested.

Claims 2, 3 and 9-15 were rejected under 35 U.S.C. § 112, first paragraph, because the specification allegedly does not enable polynucleotides with a sequence homology of 84%. This rejection is respectfully traversed.

Applicants believe that the stated 84% homology is high, not low, as alleged by the Examiner. For example, polyketide cyclase SnoaM is 73% and 71% homologous to AknW and DpsY, respectively. The genes of all of these three enzymes are able to complement non-producing *S. peucetius* mutant D2 to produce daunomycins (Hautala, A., Torkell, S., Räty, K., Kunnari, T., Kantola, J., Mäntsälä, P., Hakala, J. and Ylihonko, K., Studies on a Second and Third Ring Cyclization in Anthracycline Biosynthesis. J. Antibiot 56(2):143-153 (2003), provided herewith as Appendix F. Nucleotide sequence homology of SnoaM to AknQ and DpsY is 74 % and 73%, respectively.

No undue experimentation is required to use the claimed invention to the full extent of its scope. The predictability of the functionality of sequences with 84% homology, is not "extremely low." To the contrary, the examples cited above demonstrate that sequences with significantly lower homology are functional. Moreover, the structure of suitable sequences having at least 84% homology is

easily predicted by one of skill in the art. Therefore the claims are properly enabled, and reconsideration and withdrawal of this rejection are respectfully requested.

Claims 9, 11, 12 and 14 were rejected under 35 U.S.C. § 112, first paragraph for allegedly not enabling methods of increasing aclacinomycin production in all *Streptomyces* hosts. This rejection is respectfully traversed.

Claims 9 and 13 have been amended to recite a *Streptomyces* host producing aclacinomycins or intermediates thereof. Thus, the claims are directed to those hosts which natively produce aclacinomycins or their intermediates.

Claim 12 is amended to recite "a *Streptomyces* host producing polyketide compounds." This further limits the group of *Streptomyces*. In particular those cells which do not natively produce polyketides are excluded. This is in accordance with the observation that *Streptomyces peucetius* M18 and M90, which produce (epsilon)-rhodomycinone, are operable in accordance with the invention. Claim 15 is amended to depend from claim 12 instead of claim 13.

Although the specification provides a more detailed description for Sg4 than for Sg5, Sg5 is expected to have similar advantageous characteristics. For instance, Sg5 includes an activator, which would contribute to its having properties similar to that of Sg4.

Accordingly, reconsideration and withdrawal of this rejection are respectfully requested.

Claims 2, 3 and 9-15 were rejected under 35 U.S.C. § 102 over Raty. The Examiner noted that the instant claims were previously afforded priority only to the PCT date based on a lack of support for the 84% homology limitation. However, as noted above, the original priority application included this limitation. See Appendix A, in particular, claim 2. Therefore, the instant claims are properly entitled to the priority date of September 29, 1999, which predates the asserted public availability date of the cited reference of July 13, 2000.

Accordingly, this rejection cannot be properly maintained and withdrawal thereof is respectfully requested.

CONCLUSION

In view of the foregoing, the application is respectfully submitted to be in condition for allowance, and prompt favorable action thereon is earnestly solicited.

If there are any questions regarding this amendment or the application in general, a telephone call to the undersigned would be appreciated since this should expedite the prosecution of the application for all concerned.

If necessary to effect a timely response, this paper should be considered as a petition for an Extension of Time sufficient to effect a timely response, and please charge any deficiency in fees or credit any overpayments to Deposit Account No. 05-1323 (Docket #029381.49884).

Respectfully submitted,

July 8, 2004

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